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Do children with recurrent abdominal pain grow up to become adolescents who control their weight by fasting? Results from a UK population-based cohort

Kate Stein MRCPsych, BSc[1] | Naomi Warne PhD[2] | Jon Heron PhD[2] | Nancy Zucker PhD[3] | Helen Bould MRCPsych, DPhil[2,4]

[1]Academic Clinical Fellow in Child and Adolescent Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

[2]Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

[3]Department of Psychology and Neuroscience, Duke University, Durham, North Carolina

[4]Gloucestershire Health and Care NHS Foundation Trust, Gloucester, UK

Correspondence
Kate Stein, Academic Clinical Fellow in Child and Adolescent Psychiatry, University of Oxford; Warneford Hospital, Oxford OX3 7JX, UK.
Email: kate.stein@psych.ox.ac.uk

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Abstract

Objective: Gastrointestinal (GI) problems are common in eating disorders, but it is unclear whether these problems predate the onset of disordered eating. Recurrent abdominal pain (RAP) is the most prevalent GI problem of childhood, and this study aimed to explore longitudinal associations between persistent RAP (at ages 7 and 9) and fasting for weight control at 16.

Method: The Avon Longitudinal Study of Parents and Children (ALSPAC) is a UK population cohort of children. Childhood RAP was reported by mothers and defined as RAP 5+ (5 pain episodes in the past year) in our primary analysis, and RAP 3+ (3 pain episodes) in our sensitivity analysis. Fasting for weight control was reported by adolescents at 16. We used logistic regression models to examine associations, with adjustments for potential confounders.

Results: After adjustments, we found no association between childhood RAP 5+ and adolescent fasting for weight control at 16 (OR 1.30 (95% Confidence Intervals [CI] 0.87, 1.94) p = .197). However, we did find an association between RAP 3+ and later fasting, in the fully adjusted model (OR 1.50 [95% CI 1.16, 1.94] p = .002), and after excluding those with pre-existing anxiety (OR 1.52 [95% CI 1.17, 1.97] p = .002).

Discussion: Our findings suggest a possible independent contribution of RAP to later risk of fasting for weight control, and RAP should be enquired about in the assessment of eating disorders. However, frequency of childhood abdominal pain (as captured by ALSPAC) may be less important to long-term outcomes than functional impairment.

KEYWORDS
abdominal pain, adolescent, ALSPAC, child, cohort study, eating disorders, fasting, longitudinal, prospective, United Kingdom

1 | INTRODUCTION

People with eating disorders (ED) are known to suffer from concurrent gastrointestinal (GI) complaints (e.g., abdominal pain, constipation and bloating) (Sato & Fukudo, 2015) and there is an expanding body of evidence that suggests, for a significant group of patients, that GI symptoms may *precede* their disordered eating (Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004; Wiklund et al., 2019; Zucker & Bulik, 2020). By far the most common GI complaint in childhood is recurrent abdominal pain (RAP). This affects between 10% and 12% of 5- to 16-year-old schoolchildren (Apley & Naish, 1958; Boey, Yap, & Goh, 2000), usually with no identifiable disease pathology (Ramchandani, Hotopf, Sandhu, & Stein, 2005). The most widely accepted definition of recurrent abdominal pain, introduced by Apley, is when a child has had, "At least three bouts of pain, severe enough to affect his/her activities, over a period of at least 3 months, with attacks continuing in the year preceding examination" (Apley & Naish, 1958). However, the concept of childhood RAP has more recently (2016) been replaced by the term pediatric Functional Abdominal Pain Disorders (FAPDs) (Thapar et al., 2020). According to the Rome IV Criteria, FAPDs can be defined as when abdominal pain occurs 4 or more times a month, for at least 2 months, in either an episodic or continuous fashion, and cannot be ascribed to an inflammatory, anatomic, metabolic, or neoplastic process (Hyams et al., 1996). Pediatric FAPDs can be subclassified, utilizing the Rome IV criteria, to comprise irritable bowel syndrome, functional dyspepsia, abdominal migraine, and functional abdominal pain not otherwise specified (Hyams et al., 2016). FAPDs are thought to share the same etiology and they more recently tend to be described as disorders of GI–brain interaction (Thapar et al., 2020). Whilst the Apley definition requires children to suffer from less frequent pain than those applied for childhood FAPDs, it includes pain severity and functional impairment, so it remains useful and relates to the operational definitions used in the Rome criteria, which became available in 2005 (Rasquin-Weber et al., 1999). We believe that the RAP data used in this study, which were collected from 1991 onwards, will broadly capture all of the pediatric FAPDs, as the parents were asked a general question about their child's stomach pain without any reference to its cause or other co-morbidities. Thus, for clarity and consistency in this study, we will refer to childhood RAP.

Children with RAP tend to have more concurrent anxiety and depressive disorders (Campo, 2012; Ramchandani et al., 2006), and the presence of childhood RAP is a robust predictor of emotional disorders in adulthood (Hotopf, Carr, Mayou, Wadsworth, & Wessely, 1998; Shelby et al., 2013; Stein et al., 2017; von Gontard et al., 2015). The high association of childhood RAP with anxiety has meant that RAP has often been attributed to generalized anxiety (Campo, 2012). However, more recent research has shown that visceral hypersensitivity (i.e., increased sensitivity to GI sensations) is especially important for developing increased pain sensitivity, hypervigilance, and poor coping responses (Hazlett-Stevens et al., 2003; Labus et al., 2007). Such visceral hypersensitivity appears to be a key *independent* variable in long-term health outcomes (Labus et al., 2007; Simrén et al., 2018). The association between visceral hypersensitivity and GI symptom severity was elegantly demonstrated in a study that incorporated five large cohorts of patients with functional GI disorders. Associations between visceral hypersensitivity and GI symptom severity were still present after adjusting for anxiety, suggesting that visceral hypersensitivity makes an independent contribution to the severity of GI symptoms (Simrén et al., 2018).

It is plausible that early GI discomfort (as seen in RAP) may increase vulnerability to anorexia nervosa (AN) through processes of aversive visceral conditioning (Zucker & Bulik, 2020). Early painful GI events may sensitize children's pain pathways, leading to amplification, preoccupation, and generalization to innocuous sensations (Labus et al., 2007). In other words, children with RAP become oversensitive to and hypervigilant about their essentially normal gut sensations. The fear-avoidance model of pain predicts that children who suffer from visceral hypersensitivity may start avoiding particular foods and other activities which they associate with the prediction of later pain (Leeuw et al., 2007). Food and eating may be a particularly potent learning pathway in the context of GI pain. The act of eating requires that one penetrate a body boundary. As such, it is critical that a variety of protective responses help an organism to avoid ingestion of a potential toxin. One example is vivid visceral memories resulting from one-trial learning experiences such as food poisoning, memories that can strongly influence later avoidance behavior (Zucker & Bulik, 2020). Thus, GI sensations may be potent learning signals, causing individuals to become highly anxious and preoccupied with food choices, and this may contribute to the development of disordered eating patterns (Labus et al., 2007; Simrén et al., 2018).

Figure 1 illustrates how a child with RAP can develop fearful reactions to normal GI sensations, and start to avoid foods which they associate with the pain. Based on the fear-avoidance model of pain (Leeuw et al., 2007), the model predicts that those suffering from childhood RAP will be more likely to avoid food by fasting to control their weight. Within the model, we propose that RAP and anxiety are intrinsically linked, and co-exist on the potential causal pathway to disordered eating

A clinical study from Sweden showed that childhood GI complaints (defined as severe abdominal pain, early feeding problems, or in-patient treatment for GI problems) were more common in their sample of 51 adolescent females with anorexia nervosa than in healthy controls (Råstam, 1992). Also, in adult women with bulimia nervosa, those who recalled early childhood GI issues were found to have an earlier age of onset of their eating disorder and of the symptom of self-induced vomiting compared with women with no childhood GI complaints (Gendall et al., 2005). A case–control study (Quick, McWilliams, & Byrd-Bredbenner, 2012) matching individuals with a medical condition typically treated with a dietary manipulation (e.g., diabetes, irritable bowel syndrome) to healthy control subjects, found that those with a medical condition were twice as likely to be diagnosed with an eating disorder (Quick et al., 2012). In a systematic review, Conviser, Fisher, and McColley (2018) found that reported age of onset of a medical condition requiring dietary manipulation often preceded that of an eating disorder, but no prospective data about this relationship were reported in regard to GI disorders generally or RAP specifically. To our knowledge, no study has assessed the prospective association between childhood RAP and subsequent fasting behaviors. Research using longitudinal data that have been

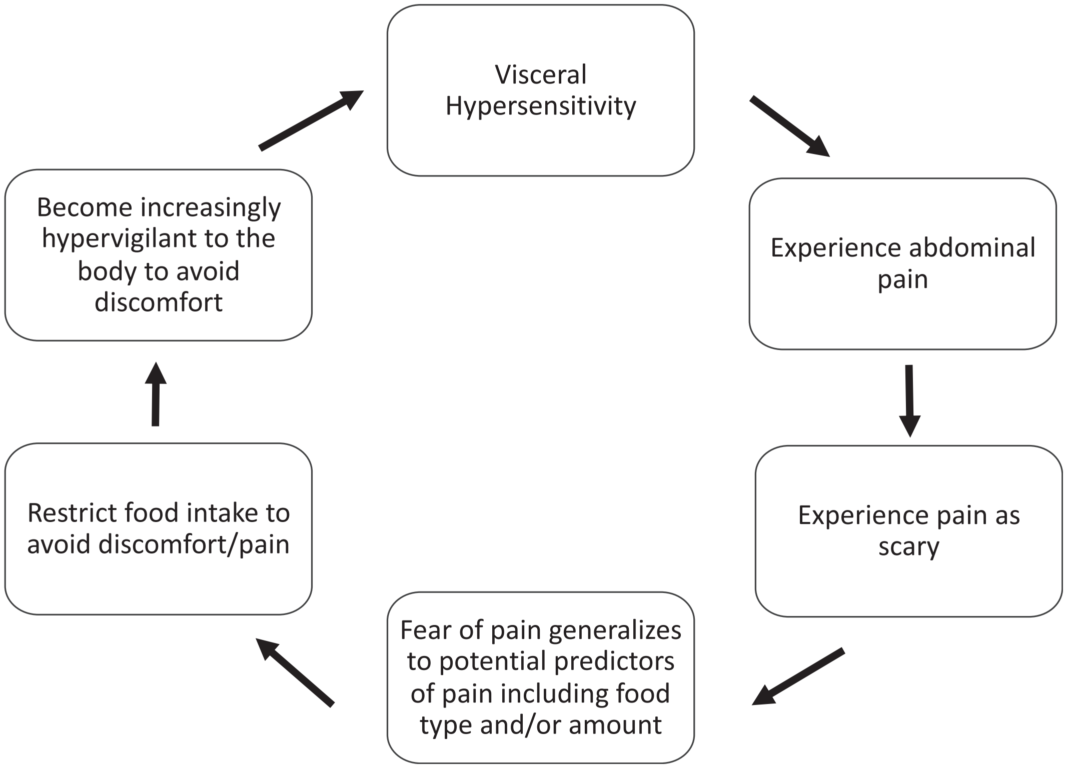

FIGURE 1 Fear avoidance model of abdominal pain and food restriction

collected prospectively is needed to avoid the challenges of bias in retrospective designs. Furthermore, population-based studies can help us to study more people with these difficulties, as many people with harmful fasting behaviors do not seek medical help (Solmi et al., 2016). Moreover, population studies consistently find that many people meeting diagnostic criteria for eating disorders do not receive any kind of treatment (Swanson et al., 2011).

We therefore examined the prospective relationship between childhood RAP and fasting behavior in adolescence using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK population-based cohort (Boyd et al., 2013). We hypothesized that persistent childhood RAP (present at both ages 7 and 9) would be associated with an increased risk of fasting to control weight at age 16. In order to explore the complex relationship between RAP and anxiety, we subsequently excluded children with a pre-existing anxiety diagnosis at age 7, to see if any potential relationship between RAP and fasting to control weight remained.

2 | METHOD

2.1 | Sample

Pregnant women resident in Avon, UK with expected dates of delivery from 1st April 1991 to 31st December 1992 were invited to take part in ALSPAC. The initial number of pregnancies enrolled was 14,541 (for these at least one questionnaire has been returned or a "Children in Focus" clinic had been attended by 19th July 1999). Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age (Boyd et al., 2013; Fraser et al., 2013).

When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 24 is 913 (456, 262, and 195 recruited during Phases II, III and IV respectively), resulting in an additional 913 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper and its update (Boyd et al., 2013). The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 fetuses. Of these 14,901 were alive at 1 year of age.

A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group was chosen at random from the last 6 months of ALSPAC births (1,432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.

The study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees: http://www.bristol.ac.uk/alspac/researchers/research-ethics/. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time (Boyd et al., 2013; Fraser et al., 2013).

We first excluded multiple births from the dataset, to remove any possible familial clustering effects. In this study, we present results on individuals with complete case data (*n* = 3,001) on exposures, outcome and potential confounders, as well as individuals with imputed data (*n* = 8,041). Please see our Figure 2 "Flowchart of Attrition."

2.2 | Measures

2.2.1 | Exposure: Recurrent abdominal pain (RAP) in childhood

ALSPAC collected childhood abdominal pain data by asking the parents the following questions:

1. *Have there been times when your child seems to have had a pain in their stomach in the past 12 months? (yes/no)*
2. *How many separate times has this happened in the past 12 months? (Answer: Once, Twice, 3 or 4 times, 5 or more times, or Don't know)*

ALSPAC sent questionnaires to mothers when their children were 3, 4, 7 and 9 years old. We focused on RAP at age 7 years and 9 years, as RAP in childhood peaks at age 7–9 years (Ramchandani et al., 2005). In line with previous research (Ramchandani et al., 2005; Stein et al., 2017), the RAP exposure measure for our primary analysis included all children reported as having 5 or more episodes of abdominal pain (RAP 5+) in the past year, because this most closely matched Apley's definition of 3 episodes of abdominal pain in 3 months (Apley & Naish, 1958). The ALSPAC dataset, however, differs from Apley's definition, because it only asks about pain frequency, and it does not ask parents about the intensity of their child's pain or their functional impairment. Since previous research highlights the association between avoidant behavior, impairment, and parameters of pain beyond frequency (Walker, Baber, Garber, & Smith, 2008), we did not want to miss relevant data by only capturing those children with the most frequent pain. We therefore conducted a sensitivity analysis including data from children who experienced 3 or more episodes of pain (RAP 3+) per year.

2.3 | Outcome: Fasting to control weight

Data on "fasting to control weight" behaviors were gathered at age 16, using questions adapted from the Youth Risk Behavior Surveillance System questionnaire (Kann et al., 2018). The adolescents were asked the following question:

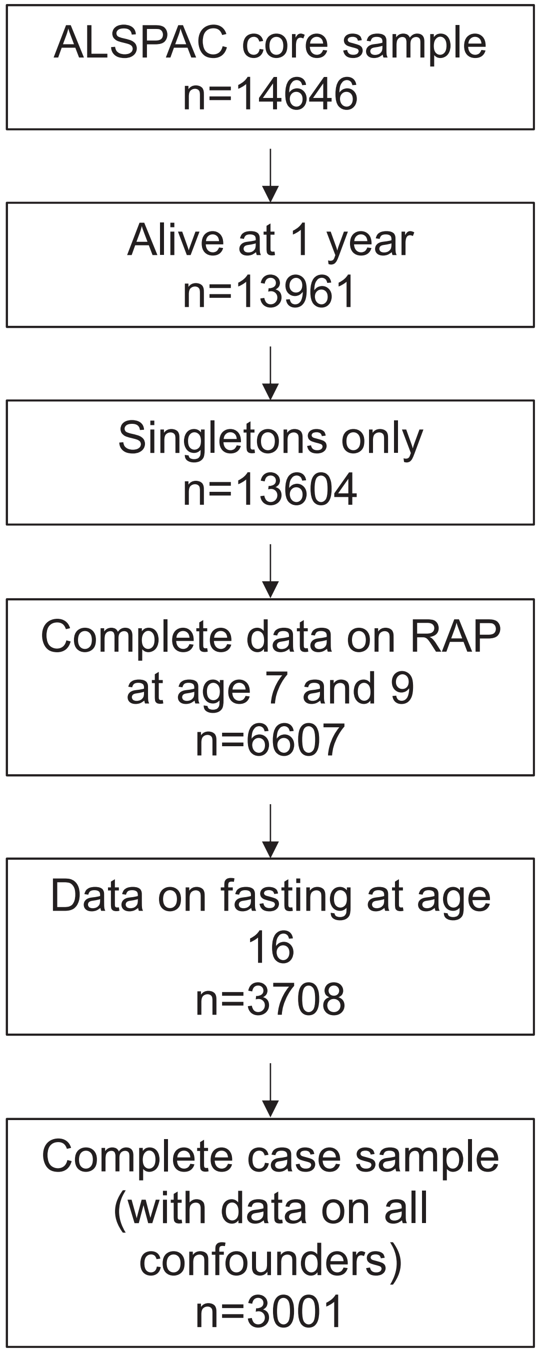

FIGURE 2 Participant attrition

> During the past year, how often did you fast (not eat for at least a day) to lose weight or avoid gaining weight? (Answer: Never; Less than once a month; Monthly; Weekly)

We converted this to a binary (yes/no) variable of whether the adolescents had ever engaged in fasting behavior over the past year. The question has been validated in comparison with the Eating Behaviors Interview in a population-based sample of adolescents (Field et al., 2004).

2.4 | Confounders

We adjusted for gender and various maternal factors (socioeconomic status [SES], maternal educational level, maternal anxiety and depression). Gender was included as a confounder because girls experience considerably higher rates of both RAP (Ramchandani et al., 2005) and fasting to control weight (Lindberg & Hjern, 2003).

We included maternal SES because high SES has been found to be associated with EDs in offspring (Lindberg & Hjern, 2003). RAP is also more common in children of mothers with higher educational attainment and social class (Ramchandani et al., 2005). Maternal SES was defined as an ordinal variable [I (professional), II (managerial/technical), IIIN (skilled non-manual), IIIM (skilled manual), IV (partly skilled), V (unskilled)]. Maternal educational level has been associated with EDs in offspring (Ahrén et al., 2013) and was included from maternal report at 32 weeks' gestation. Mother's highest educational qualification was coded as either advanced level qualifications obtained at age 18 or degree (1), or lower (ordinary level qualifications or certificate of secondary school education obtained at age 16, vocational qualification or none) (0).

Since RAP was determined via maternal reports, we controlled for maternal anxiety (a binary variable of mothers in the top 20% (≥8) on the Crown Crisp Experimental Index anxiety subscale (Birtchnell, Evans, & Kennard, 1988) (during pregnancy, at 32 weeks' gestation) and maternal depression (a binary variable of those scoring ≥12 on the Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987) (measured 8 weeks after birth) as previous research has shown both of these measures to be correlated with both RAP (Ramchandani et al., 2007) and EDs in offspring (Bould et al., 2015).

Given the complex relationship between RAP and anxiety, we also repeated the analyses, excluding individuals with a Development and Wellbeing Assessment (DAWBA) anxiety diagnosis at age 7. We excluded these individuals to ensure that anxiety was not a *pre-cursor* to the RAP. However, Childhood RAP and anxiety are highly co-morbid and intrinsically linked on the potential causal pathway to disordered eating. Mothers reported child anxiety on a questionnaire version of the Development and Wellbeing Assessment (DAWBA) (Goodman et al., 2000) when the child was 7. Responses were coded in line with DSM-IV anxiety diagnoses (separation anxiety disorder, specific phobia, social phobia, posttraumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, and anxiety disorder not otherwise specified). We used a derived binary (yes/no) variable for any anxiety disorder.

2.5 | Statistical analysis

All analyses were conducted using Stata version 16 (StataCorp, 2019). First, we describe sample characteristics in complete cases, those with all available data, and the imputed dataset (see Table 1). We used logistic regression models to examine associations between persistent RAP 5 + (5 or more episodes per year) at ages 7 and 9 years and subsequent fasting at age 16. Initially, we examined unadjusted associations, before sequentially adjusting for gender (Model A), maternal social class and education (Model B), and maternal anxiety and depression (Model C). We conducted a sensitivity analysis using persistent RAP 3+ at 7 and 9 years and fasting at 16. Given the complex relationship between RAP and anxiety, we repeated these analyses in individuals without a DAWBA anxiety diagnosis at age 7.

2.6 | Missing data

Due to missing data on RAP, fasting, and confounding variables, the complete case analysis sample was smaller than the original starting sample. Thus, to avoid biased or underestimated results, we examined the potential impact of missing data by imputing data using the multivariate imputation by chained equations (MICE) approach (White & Royston, 2009) to boost the sample to those responding to the age 7 questionnaire with anxiety diagnosis. This was done using the "mi impute chained" command in Stata which assumes data is missing at random (MAR), that is, differences between respondents and non-respondents can be explained by other observed data. Imputation models included variables required for analysis in addition to auxiliary variables related to missingness. Auxiliary variables included in the models were RAP at 3 and 4 years, BMI at ages 7 and 15, parent-reported child fear of weight gain and fat avoidance at ages 13 and 16, child-reported body dissatisfaction at age 14, and parent-reported child depressive symptoms at age 11. Fifty imputed datasets were created for each of two different imputation models—one for all participants responding to the age 7 anxiety diagnosis questionnaire (n = 8,041), and another for all participants without an anxiety diagnosis at age 7 (n = 7,791).

3 | RESULTS

Table 1 provides descriptive information about the participants with complete case and partial data for the exposure and outcome variables, including the numbers in the imputed data.

In complete case analyses, 186 of 3,001 children (6.2%) were reported by their parents as having persistent abdominal pain at both ages 7 and 9 years. When we defined RAP as 3+ instead of 5+ episodes in the past year, the number of children with persistent pain increased to 571 of 3,001 (19.0%). 380 of the 3,001 adolescents (12.7%) reported fasting for more than 1 day, to lose weight. In the complete case sample of 3,001, 494 (16.5%) of mothers suffered from an anxiety disorder, and 73 (2.73%) children suffered from an anxiety disorder at age 7.

In the complete case sample, 18.82% (35/186) of children with RAP5+ reported fasting at age 16, compared to 12.26% (345/2,815) of individuals without RAP5+. Similarly, 18.74% (107/571) of children with RAP3+ reported fasting at age 16 compared to 11.23% (273/2,430) without RAP3+.

3.1 | Persistent childhood RAP (5+) and fasting at 16

In our primary analysis, defining RAP as 5 or more episodes of abdominal pain in the past year, we found an initial association between RAP

TABLE 1 Sample characteristics for participants with complete case and all available data

	Available data (*N* varies by variable)	Complete case (*N* = 3,001)	Imputed data (*n* = 8,041)
Persistent RAP at 7 and 9 years (*N*, %)	359/6607 (5.43%)	186 (6.20%)	5.51%
Fasting to control weight at 16 (*N*, %)	624/4726 (13.20%)	380 (12.66%)	11.57%
Anxiety diagnosis at 7 years (*N*, %)	250/8041 (3.11%)	73 (2.43%)	5.14%
Gender, female (*N*, %)	6589/13604 (48.43%)	1,693 (56.41%)	48.68%
Maternal social class, I (*N*, %)	578/9794 (5.90%)	286 (9.53%)	[a]
Maternal education, A level or higher (*N*, %)	4276/12090 (35.37%)	1,592 (53.05%)	41.40%
Maternal anxiety (*N*, %)	2601/11407 (22.80%)	494 (16.46%)	20.68%
Maternal depression (*N*, %)	1486/11416 (13.02%)	296 (9.86%)	11.85%

Note: Complete case = data for all RAP exposures, fasting to control weight, and all covariates; RAP = Recurrent Abdominal Pain defined as 5+ instances of stomach pain in the last 6 months.
[a]Social class could not be computed in the imputational model.

TABLE 2 Associations between persistent RAP (defined as 5+ episodes of abdominal pain in the past year) and fasting to control weight at age 16

	Unadjusted		Adjusted model A		Adjusted model B		Fully adjusted model C	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Persistent RAP (5+) at 7 and 9 years (complete cases, *n* = 3,001)	1.66 (1.13, 2.44)	.011	1.28 (0.86, 1.91)	.216	1.31 (0.88, 1.95)	.186	1.30 (0.87, 1.94)	.197
Persistent RAP (5+) at 7 and 9 years (imputed dataset, *n* = 8,041)	1.37 (0.99, 1.91)	.060	1.04 (0.73, 1.46)	.841	1.06 (0.75, 1.49)	.761	1.04 (0.74, 1.48)	.822
Analyses restricted to individuals without DAWBA anxiety diagnosis at age 7								
Persistent RAP (5+) at 7 and 9 years (complete cases, *n* = 2,928)	1.61 (1.08, 2.38)	.018	1.25 (0.83, 1.88)	.276	1.27 (0.85, 1.92)	.244	1.27 (0.84, 1.91)	.254
Persistent RAP (5+) at 7 and 9 years (imputed dataset, *n* = 7,791)	1.35 (0.92, 1.98)	.130	1.01 (0.67, 1.51)	.972	1.03 (0.69, 1.54)	.891	1.02 (0.68, 1.53)	.931

Note: Model A = adjusted for gender; Model B = adjusted for gender, maternal social class and maternal education; Fully adjusted Model C = adjusted for gender, maternal social class, maternal education, maternal anxiety, and maternal depression; RAP = Recurrent Abdominal Pain defined as 5+ episodes of stomach pain in the last 12 months.

TABLE 3 Sensitivity analysis: Associations between RAP (defined as 3+ episodes of abdominal pain in the last year) and fasting to control weight at age 16

	Unadjusted		Adjusted model A		Adjusted model B		Fully adjusted model C	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Persistent RAP (3+) at 7 and 9 years (complete cases, *n* = 3,001)	1.82 (1.43, 2.33)	<.001	1.49 (1.15, 1.92)	.002	1.50 (1.16, 1.94)	.002	1.50 (1.16, 1.94)	.002
Persistent RAP (3+) at 7 and 9 years (imputed dataset, *n* = 8,041)	1.53 (1.23, 1.92)	<.001	1.27 (1.00, 1.62)	.051	1.29 (1.02, 1.64)	.040	1.28 (1.01, 1.63)	.041
Analyses restricted to individuals without DAWBA anxiety diagnosis at age 7								
Persistent RAP (3+) at 7 and 9 years (complete cases, *n* = 2,928)	1.85 (1.44, 2.37)	<.001	1.50 (1.16, 1.95)	<.001	1.52 (1.17, 1.97)	.001	1.52 (1.17, 1.97)	.002
Persistent RAP (3+) at 7 and 9 years (imputed dataset, *n* = 7,791)	1.58 (1.27, 1.97)	<.001	1.31 (1.05, 1.65)	<.001	1.34 (1.07, 1.67)	.011	1.33 (1.05, 1.67)	.021

Note: Model A = adjusted for gender; Model B = adjusted for gender, maternal social class and maternal education; Fully adjusted Model C = adjusted for gender, maternal social class, maternal education, maternal anxiety and maternal depression; RAP = Recurrent Abdominal Pain defined as 3+ episodes of stomach pain in the last 12 months.

5+ and fasting to control weight at age 16 in the unadjusted model (OR 1.66 [95% CI.1.13, 2.44], p = .011) (Table 2). However, this association decreased after adjusting for gender, and included the possibility of no association (OR 1.28 [95% CI.0.86, 1.91], p = .216) (Table 2). In the fully adjusted model (controlling for gender, maternal education and SES, and maternal anxiety and depression) we found no evidence for an association between RAP 5+ and fasting to control weight (OR 1.30 [95% CI.0.87, 1.94], p = .197) (Table 2).

We did not find an association after we excluded those with a DAWBA-diagnosed anxiety disorder at age 7 (OR 1.27 [95% CI.0.84, 1.91], p = .254) (Table 2). Findings from imputed data were consistent with complete case results.

3.2 | Persistent childhood RAP (3+) and fasting at 16

In our sensitivity analysis, defining RAP as 3 or more episodes of abdominal pain in the past year, we found an association between RAP 3+ and fasting to control weight at 16, and this association remained after adjusting for confounding variables (OR 1.50 [95% CI.1.16, 1.94], p = .002) (Table 3).

The association also remained after we excluded those with a DAWBA-diagnosed anxiety disorder at age 7 (OR 1.52 [95% CI.1.17, 1.97], p = .002). The findings were also unchanged when we conducted the analyses using the imputed datasets (Table 3).

4 | DISCUSSION

In our primary analysis, we did not find evidence of a relationship between persistent childhood RAP (defined as 5+ episodes in the past year at age 7 and 9) and fasting to control weight at 16, once we adjusted for gender. This suggests that the apparent relationship seen in the unadjusted model was explained by the strong associations between female gender and both childhood RAP and adolescent fasting to control weight. However, a different picture emerged in our sensitivity analysis. When we defined RAP as 3+ episodes of pain in the past year at age 7 and 9, we found that RAP 3+ *was* associated with fasting to control weight at 16, and this association persisted following adjustment for confounding variables, and in an analysis excluding those with a DAWBA anxiety diagnosis at age 7.

There are a number of possible reasons why we found an association between “fasting to control weight” with RAP 3+ but not RAP 5+. One explanation could be that pain frequency (as captured by ALSPAC) may be less important to long-term outcomes than pain severity, pain distress and/or the child's functional impairment resulting from their pain. For example, previous research has demonstrated an association between a child's avoidant coping style when experiencing pain and their functional disability, and this link may be especially relevant to the association between RAP and fasting to control weight, (Walker et al., 2008) in that either there is an important mediator between RAP and fasting (e.g., pain distress, fear of weight-gain/intolerance of bloating) that would be a crucial target for intervention or that another feature of pain (e.g., pain intensity) was related to more functional impairment. Thus, having a cut off of RAP 3+ could have captured children with more emotional or functional impairment (e.g., school avoidance, social withdrawal) despite having fewer episodes of pain.

Another explanation for an association with RAP 3+ but not RAP 5+ could be the contribution of the Non-Extreme Response bias, whereby participants tend to avoid selecting the extreme endpoints on a scale, preferring to select the middle values (Liu et al., 2017). Thus, by asking the parents to report their child's RAP as 5+ episodes in the past year, we may have inadvertently missed out on important and relevant data.

Alternatively, it could be that the children with the more frequent abdominal pain (RAP 5+) have some other underlying cause that might get treated prior to adolescence. This seems unlikely, however, as there is robust evidence that childhood RAP is rarely due to a disease process (Ramchandani et al., 2005; Thornton et al., 2016). RAP may arise from a variety of causes and this is highlighted by the conceptualization of RAP as a disorder of GI-brain interaction. The complex interaction between GI physiology and top-down influences, such as threat interpretations of somatic sensations, must be taken into account when creating a formulation of childhood RAP. From this standpoint, bottom-up influences (e.g., delayed gastric emptying, constipation, aberrant immune responses) would enrich our understanding of an individual's unique pain/eating pathway and potentially help us to develop more personalized intervention strategies. Also, because of this complexity, the number of episodes of abdominal pain (e.g., 3 vs. 5 episodes) is but one facet to take into consideration in understanding an individual's pain experience and how they choose to manage that experience (e.g., as with restricting eating).

The other possibility is that our results may be due to chance. We think this is unlikely because the association between childhood RAP 3+ and fasting to control weight at 16 held after adjusting for a variety of confounders known to be associated with both our exposure and outcome.

Various mechanisms might explain the possible association between less frequent, but nonetheless persistent, childhood RAP and adolescent fasting to control weight. First, unpleasant GI experiences could lead children to become oversensitive to and hypervigilant about essentially normal GI sensations (Simrén et al., 2018). Consuming food is inevitably associated with GI sensations, so a desire to avoid uncomfortable GI feelings could contribute to beliefs about the avoidance of certain foods, food amounts, or periods of food abstinence as contributing to improvement in GI sensations (Wiklund et al., 2019). Second, such behaviors could have physiological and metabolic consequences such as alterations in the composition of the intestinal microbiome. In a cohort of children with functional GI problems, their microbiome composition correlated with abdominal pain severity and frequency (Saulnier et al., 2011). Also, there is evidence that in patients with AN, levels of depression, anxiety, and eating disorder psychopathology were associated with composition and diversity of their gut bacteria (Kleiman et al., 2015).

4.1 | Strengths and limitations

The major strengths of our study are the large sample size, prospective collection of data on RAP and confounders, and the long duration of follow up. Using this study design, we have also been able to include more participants. Many of these will have experienced RAP and unhealthy fasting behaviors, but may never have come to the attention of doctors (Solmi et al., 2016).

These results need to be interpreted in the light of some limitations. The diagnostic criteria for RAP have been subject to some debate (Thapar et al., 2020). Apley's original definition of childhood RAP (Apley & Naish, 1958), which corresponds best to the ALSPAC data collected in 1991, requires children to suffer from less frequent pain than the Rome IV criteria, and it does not include a detailed assessment of their functional impairment. Thus, it is possible that the group we describe here was affected less severely than those in other studies (Hyams et al., 1996; Thapar et al., 2020). However, we think this is unlikely because a previous ALSPAC study showed that nearly one quarter (23.5%) of the children with RAP had been taken to the doctor because of their abdominal pain (Ramchandani et al., 2005).

The most widely used measure of eating disorder psychopathology is the Eating Disorder Examination Questionnaire (EDE-Q), which defines "food avoidance" as, "Going without food for a period of 8 or more waking hours in order to influence weight or shape." Previously, the DSM-IV criterion of "fasting" defined it as "not eating anything at all for 24 hr" (American Psychiatric Association, 1994) but this is now considered to be overly restrictive (Cooper & Fairburn, 2003). In our study, 12.66% of 16-year-olds stated that over the past year, they fasted (did not eat for at least a day) to lose weight. Whilst this is quite a stringent measure in terms of duration of fasting, it corresponds to other non-selected population samples (Carter, Stewart, & Fairburn, 2001), suggesting that we were broadly capturing the same people. However, we may have missed adolescents with milder, but still impairing fasting behaviors. On the other hand, fasting for a day does not in itself indicate a clinically diagnosable eating disorder.

As with any population based prospective cohort, sample attrition is a problem (see Figure 2). We used multiple imputation to account for missing data, but this technique is limited by our pre-existing knowledge of which factors to explore. Another potential limitation is that RAP was determined by maternal report. Nevertheless, adjusting for relevant maternal factors that may have influenced their reporting did not substantially alter the results. In addition the ALSPAC sample is a predominantly white British cohort (Boyd et al., 2013), so results may not be applicable to other ethnic groups.

4.2 | Clinical implications

Our findings have a number of clinical implications and directions for future research. For example, we might want to consider routinely enquiring about childhood RAP in eating disorder assessments, not just those concerning Avoidant and Restrictive Food Intake Disorder (ARFID) (Zucker & Bulik, 2020) and routinely assessing disordered eating in patients with GI disorders (Zucker & Bulik, 2020). Also, our findings suggest that our cognitive-behavioral interventions for patients with eating disorders might be enriched by incorporating an exposure component that targets patients' anxiety and fear associated with their visceral sensations, and helps them to accept and better tolerate their physiology (Plasencia et al., 2019; Zucker et al., 2019).

5 | CONCLUSIONS

To our knowledge, this is the first study to provide prospective evidence suggesting that there may be an association between childhood recurrent abdominal pain and later fasting behaviors in adolescence. By analyzing a large cohort, our findings tentatively support previous clinical studies that have found that, for a group of eating disorder patients, RAP may precede and contribute to disordered eating (Råstam, 1992; Zucker & Bulik, 2020). Our study extends previous work by suggesting that childhood RAP, may be an independent and specific risk factor for later fasting, above and beyond pre-existing anxiety.

Whilst the independent contribution of RAP to the overall risk of developing an eating disorder appears to be quite modest, coupled with anxiety and other important psychological factors it may be clinically significant and should be enquired about in the assessment and management of eating disorders.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The informed consent obtained from ALSPAC participants does not allow the data to be made freely available through any third party maintained public repository. However, data used for this submission can be made available on request to the ALSPAC Executive. The ALSPAC data management plan describes in detail the policy regarding data sharing, which is through a system of managed open access. Full instructions for applying for data access can be found here: http://www.bristol.ac.uk/alspac/researchers/access/. The ALSPAC study website contains details of all the data that are available (http://www.bristol.ac.uk/alspac/researchers/our-data/)

ORCID

Kate Stein https://orcid.org/0000-0001-8788-984X
Nancy Zucker https://orcid.org/0000-0003-2278-5008

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